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DICKSTEIN SHAPIRO LLP 1825 EYE STREET NW Washington, DC 20006-5403			EXAMINER HAGHIGHATIAN, MINA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/671,708	Applicant(s) DUGGER ET AL.	
	Examiner MINA HAGHIGHATIAN	Art Unit 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/09/08.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-18, 20-27, 29 and 48-65 is/are pending in the application.
- 4a) Of the above claim(s) 48, 49, 51-58 and 60-65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-18, 20-27, 29, 50 and 59 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>02/29/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Receipt is acknowledged of Remarks filed on 12/09/08. No claims have been amended, cancelled or added. Claims 48-49, 51-58, 60-65 remain withdrawn. Accordingly claims **13-18, 20-27, 29, 50 and 59** are being examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-18, 20-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deihl (WO 9413280) in view of Fassberg et al (EP 0656206A1) and further in view of Kanios et al (5,719,197) or alternatively in view of Physicians' Desk Reference, 1995.

Deihl teaches a **sprayable analgesic** composition comprising an analgesic compound which is absorbed into the bloodstream through the **buccal mucosa** and a pharmacologically acceptable liquid carrier. In a preferred embodiment the active agent is ibuprofen and the liquid carrier is **aqueous ethanol** (see page 3). The formulation may also contain other ingredients such as surfactants, humectants, **flavoring agents**, etc (see page 4). The table in example I shows the concentration ranges of each ingredient. Deihl fails to disclose other suitable active agents for the said formulation, or the use of other solvents including polyethylene glycol and non-polar solvent.

Fassberg discloses aerosol, formulations for oral or nasal administration, which comprise a medicament, an excipient, propellant and optionally surfactants. The suitable excipients include **alcohols, polyethylene glycols, short chain fatty acids**, etc (see page 3). Fassberg discloses that any pharmaceutically active agent which can be delivered by oral or nasal inhalation may be used. Examples include antihistamines, antiallergics, analgesics, antibiotics, steroids, bronchodilators, antihistamines, etc (see page 5, lines 42-50).

Kanios teaches compositions and methods for topical administration of pharmaceutically active agents. Topical administration means a direct contact of the formulation with tissue, such as skin or membrane, particularly the oral or **buccal mucosa** (col. 1, lines 29-59).

Kanios discloses that the composition comprises a therapeutically effective amount of at least one pharmaceutically **active agent**, a pharmaceutically acceptable **solvent** for the active agent (col. 2, lines 22-28). The solvent is preferably a polyhydric alcohol such as polypropylene glycol, ethylene glycol, also solvents including fatty acids such as oleic acid, as well as fatty esters or alcohols. The solvent is present in an amount from about 20 to 50 weight percent based on the total weight of the composition (col. 4, lines 1-49; col. 5, lines 24-66). The concentration of the solubilized active agent can range from **1 to 50%** by weight (col. 8, lines 1-9). The acceptable carrier is intended to be any suitable finite or non-finite carrier including liquids, semi-liquids or solid carriers. Thus the active agent may be admixed with carriers such as spray-solution or any non-finite carrier known in the art for delivery of active agents (col. 8, lines 54-67). Other additives may be incorporated into the formulations such as flavorings (col. 10, lines 48-56).

Kanios discloses that pharmaceutically active agents suitable for such formulation include galanthamine, lidocaine, mepivacaine, propofol, **testosterone and testosterone cypionate**, atracurium, ipratropium, amantadine, diazepam, pregabalin, primidone, clozapine, chlorpromazine, haloperidol, amitriptyline, buspirone, chlorzoxazone, cyclobenzaprine, interferon beta, estradiol, nimodipine, tacrine, carbidopa, acetylcholine, epinephrine, pergolide, doxepine, clomipramine, zolpidem, amphetamine, dextroamphetamine, methylphenidate, sumatriptan, pemoline, mazindol, desipramine, flumazenil, mesoridazine, etc (columns 13-31).

Physicians' Desk Reference teaches a testosterone emulsion or solution for injection for hormone replacement therapy.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of formulations for buccal mucosal administration of Diehl, to have looked in the art for other specific solvents suitable for spray formulations of liquid carriers, as taught by Fassberg et al, with reasonable expectations of successfully preparing suitable formulations for various therapies. Furthermore it would have been obvious to one of ordinary skill in the art to have substituted any suitable active agent for the analgesics of Diehl's buccal spray formulations as claimed, as taught by Kanios et al or Physician's Desk Reference. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims 13-18, 20-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fu et al (WO 9303751) in view of Physicians' Desk Reference.

Fu teaches compositions and methods for the sublingual or buccal administration of therapeutic agents. The compositions comprise a therapeutic agent dissolved or dispersed in a carrier which comprises a solvent, an optional cosolvent, and an oral mucosal membrane transport enhancing agent. The solvent comprises from about 50%

w/v to about 95% w/v of the carrier of a non-toxic alcohol. Non-alcohols useful in the said formulations include ethanol, isopropanol, stearyl alcohol, propylene glycol, polyethylene glycol and the like. Most preferred alcohol is ethanol. The cosolvent is selected from water (page 4, lines 12-26). Essential or volatile oils such as peppermint oil, spearmint oil, menthol, etc, are added in a concentration of between about 1 and 5% w/v (page 5, lines 4-10). The said liquid compositions are formulated in a liquid spray or a liquid drop (page 6, lines 1-2). Fu et al, disclosing leuprolide acetate, lacks teachings on testosterone.

Physicians' Desk Reference teaches a testosterone emulsion or solution for injection for hormone replacement therapy.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of formulations for buccal mucosal administration of Fu et al, to have looked in the art for other specific active agents suitable for spray formulations of liquid carriers, as taught by Physicians' Desk Reference, with reasonable expectations of successfully preparing suitable formulations for various therapies. Furthermore it would have been obvious to one of ordinary skill in the art to have substituted any suitable active agent as taught by Physicians' Desk Reference for the active agents of Fu et al's buccal spray formulations as claimed. In other words, the claims would have been obvious because the substitution of one

known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims 50 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fu et al (WO 9303751) in view of Physicians' Desk Reference as applied to claims 13-18, 20-27 and 29 above, and further in view of Lee et al (6,512,002).

The combined references, discussed above, lack specific disclosure on a method of stimulating erythropoiesis in a patient.

Lee et al discloses methods and pharmaceutical compositions useful in treatment of conditions that are responsive to the elevation of testosterone levels in the body. The said conditions include stimulation of erythropoiesis (abstract and col. 7, lines 15-36).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented Lee's disclosure of treating various disorders and conditions responsive to testosterone therapy to the disclosure of the combined references with the reasonable expectations of increasing options for patients and health care providers by preparing a safe, easy to use spray formulations. In other words, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed with predictable results.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **13-18, 20-27, 29, 50 and 59** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,110,486. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. In other words, claims 13-29 are generic to all that is recited in claims 1-9 of U.S. Patent No. 6,110,486. Specifically, the buccal spray composition comprising a steroidal hormone, testosterone and a polar solvent recited in claims of instant Application are anticipated by the method of administering the same composition recited in claims of 1-9 of U.S. Patent No. 6,110,486.

Claims **13 and 21** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,676,931 in view of Physician's Desk Reference. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. In other words, claims 13-29 are generic to all that is recited in claims 1-2 of U.S. Patent No. 6,676,931. Specifically, the buccal spray composition comprising a steroidal hormone, testosterone and a polar solvent recited in claims of instant Application are anticipated by the method of administering the compositions recited in claims of 1-2 of U.S. Patent No. 6,676,931 comprising cyclosporine and ondansetron hydrochloride. Physician's desk Reference teaches solutions of testosterone.

Claims **13-18, 20-27, 29, 50 and 59** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,955,098. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. In other words, claims 13-29 are generic to all that is recited in claims 1-18 of U.S. Patent No. 5,955,098. Specifically, the buccal spray composition comprising a steroidal hormone, testosterone and a polar solvent recited in claims of instant Application are anticipated by the compositions and method of administering the same composition recited in claims of 1-18 of U.S. Patent No. 5,955,098.

Claims **13-18, 20-27, 29, 50 and 59** are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 27-34, 54-59 and 80-82 of co-pending Application No. 09/537,118 in view of Physicians' Desk Reference. The double patenting rejection is proper because the examined claims and the reference claims are substantially the same. The difference is that claims of the co-pending Application '118 do not recite testosterone as the active agents. However, Physicians' Desk Reference teaches a testosterone formulation for injection. Thus it would have been obvious to one of ordinary skill in the art to have replaced the active agents of the co-pending Application '118 with the hormone, testosterone as taught by the Physicians' Desk Reference to provide a new dosage form and a new option for treating patients.

This is a provisional obviousness-type double patenting rejection.

Claims **13-18, 20-27, 29, 50 and 59** are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims of co-pending Application Nos. 10/230,060; 10/230,072; 10/230,059; 10/230,086; 10/230,080; 10/230,075; 10/230,073; 10/671,709; 10/671,717; 10/671,715; 10/671,719; 10/671, 710; 10/726,625; 10/726,585; 10/834,815; 10/663,817 and 10/928,997 in view of Swaminathan et al (WO 9733621). The double patenting rejection is proper because the examined claims are obvious over the reference claims. The difference between claims of the instant application and the claims of the reference applications is the active agents. For example, Application 10/230,075 recites active agents such as anti-

arrhythmics, anti-hypertensives, heart regulators, vasodilators, etc. Application 10/230,059 recites active agents such as anti-opioids, anti-migraines, pain control agents, etc. Application 10/663,817 recites active agents such as sleep inducers, antivirals, antibiotics, antiasthmatics, antiemetics, etc. It is also noted that many such classes of active agents are common or overlap with the agents of the instant application. Swaminathan et al (WO 9733621) teaches that various active agents can be used in the said solvent system for administration. Thus it would have been obvious to one of ordinary skill in the art to have substituted one active for the other in the same solvent system for the same method of administration.

This is a provisional obviousness-type double patenting rejection.

Pertinent Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

1) Oguri et al (JP 02-026661) teaches formulations for aerosol delivery comprising an active agent and a liquid carrier. Suitable active agents include analgesics and carrier formulations include polar and non-polar solvents and other agents. Carrier formulations may comprise a mixture of a polar and a non-polar solvent. Polar solvents include water, alcohols such as ethyl alcohol, propylene glycols. Non-polar solvents include hydrocarbons or halogenated hydrocarbons are suitable. Menthol is one of flavors used.

2) Kim (6,143,329) teaches aqueous-based pharmaceutical compositions comprising an active agent such as triamcinolone, purified water, Polysorbate and dextrose (see example 1). The said formulations are placed in a spray bottle for delivery to the surface of mucosa.

Response to Arguments

Applicant's arguments filed 12/09/08 have been fully considered but they are not persuasive.

Applicant argues that Deihl would not have been considered a credible or relevant teaching because "each spray is 50 microliters and contains 1 milligram of acetaminophen or ibuprofen. This treatment is repeated once after five minutes. That is, Deihl teaches a total dose of 4-8 milligrams of acetaminophen or ibuprofen". Applicant however agrees that that "Deihl purports to teach a sprayable analgesic composition where an analgesic is capable of being absorbed into bloodstream through the buccal mucosa" and that compositions comprise acetaminophen or ibuprofen in an aqueous ethanol base. This is not commensurate with the scope of claims. Claims are drawn to a method of **administering** testosterone comprising spraying the oral mucosa a composition comprising testosterone in an amount between 0.005 and 55% and a polar solvent in an amount between 30 and 99.69% both by weight of the composition. The formulation exemplified by Deihl (example 1) comprises about 1.93% acetaminophen and about 51.87% a polar solvent mix of ethanol and water. Thus Deihl is clearly teaching a composition comprising an active agent and the polar solvent in amounts

that overlaps the required amounts in the instant claims. Deihl teaches and Applicant agrees, delivery of the said sprayable formulation to the oral mucosa for absorption through the buccal mucosa. References such as Fassberg, Kanios or Drug Facts and Comaprison have been employed to show that formulations such as those taught by Deihl may include any pharmaceutically active agent. Thus it has been established that Deihl in view of the cited references has clearly met the instant claims. In other words Applicant's arguments are not commensurate with the scope of claims because instant claims do not require any therapeutic dosage, a percent bioavailability or degree of effectiveness.

Applicant's argument that Diehl does not teach a therapeutic amount is not persuasive because Deihl specifically compares oral dosages and buccal dosages and teaches that patients need less medicaments for buccal absorption than they would for oral (gastrointestinal) absorption. Diehl discloses that as little as 1/20th of an oral dose of a medicament may be needed for buccal administration. Thus it is disclosed that Diehl's dosage is at a therapeutic level. Also as stated above, the amounts disclosed in Diehl's example is within a concentration range claimed as "therapeutic amount" by Applicant. Thus the limitations are met.

Applicant argues that according to Remington, 19th ed. "when only small amounts of drugs are required to gain access to the blood, the buccal route may be satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route". This is neither persuasive nor commensurate with the scope of claims. Various

references e.g. Deihl, Fassberg and Cassidy et al, 1993, *Controlled buccal delivery of buprenorphine* (copy provided) have shown that many different active agents such as analgesics, polypeptides, antibiotics, etc, can successfully be administered to the buccal mucosa. Also there is no criticality disclosed by the Applicant in spraying testosterone to the oral mucosa. In fact as seen in cited references and many co-pending applications, it is obvious that different active agents can be included in the same formulation base and successfully sprayed in the oral mucosa. Therefore substituting different active agents in the same solvent formulation is an obvious variation and does not alter the scope of the claim.

Applicant argues that Fassberg is related to an inhalation aerosol comprising a propellant and does not disclose a method of delivery of a propellant-free spray to the buccal mucosa. Applicant also argues that Kanios teaches an intermediate composition that is made into a "finished dosage form" by applying a flexible backing, and that Kanios does not teach buccal spray method of administration. While Applicant's statements here are correct, the arguments are not persuasive. Fassberg and Kanios are supplementary art to provide teachings on what is missing in the primary art. Fassberg and Kanios teach solution formulations comprising various active agents, solvents and excipients and one of ordinary skill in the art would be motivated to combine the said solvents and active agents to improve on the stability, delivery or effectiveness of the formulations.

Applicant argues that Fu et al teaches compositions for sublingual delivery of specific polypeptides and in the presence of a permeation enhancer. This is not

persuasive because Fu teaches sublingual delivery of formulations comprising a therapeutic agent, particularly polypeptides. Also it is noted that instant formulations employ the open-ended language of “comprising” and do not exclude permeation enhancers. Thus presence or absence of the permeation enhancers is not relevant to the examination of instant claims here.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616